Executive functioning deficits in children with Neurofibromatosis Type 1: The influence of intellectual and social functioning

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ABSTRACT

The aim of this study was to provide a broad picture of Executive Functioning (EF) in NF1 children, while taking into account their lower average IQ and increased Autism Spectrum Disorder (ASD) symptoms. This was done by administering an extended battery of tasks and questionnaires, designed to reduce task impurity, that measures five EF domains (inhibition, cognitive flexibility, working memory, generativity and planning) in a laboratory setting and in daily life. Data are presented for 42 age- and gender-matched NF1, 52 typically developing, and 52 ASD children (8-18 years). Our results indicated that although EF is highly influenced by IQ and severity of ASD symptoms, EF deficits seem to be a core feature of NF1 and not merely a secondary effect of a lower IQ and/or increased ASD symptoms. However, additional research is needed to confirm these findings.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common autosomal dominant genetic disorder affecting approximately 1 in 2700 newborns of which 50% are *de novo* cases (Evans et al., 2010). It is part of the RAS-opathy group of disorders and is caused by a mutation in the *NF1* gene encoding neurofibromin, which is a negative regulator of the RAS (Rat sarcoma) / MAPK (Mitogen Activated Protein Kinase) pathway. NF1 is characterized by various manifestations such as café-au-lait spots, axillary or inguinal freckling, Lisch nodules, and neurofibromas. In addition, bony abnormalities and optic pathway gliomas are observed (National Institutes of Health (NIH), 1988).

Besides these features, NF1 children also display *behavioral and cognitive problems*. At the behavioral level, NF1 children present with a high level of internalizing problems (such as anxiety, depression, withdrawn behavior) and externalizing problems (such as attention problems and aggressive behavior; Graf et al., 2006; Noll et al., 2007). In addition, Attention-Deficit-Hyperactivity-Disorder (ADHD) affects around half of all children with NF1 (Mautner et al., 2002). More recently, specific attention was paid to the increased frequency of social problems in NF1 with the co-occurrence of NF1 and Autism Spectrum Disorder (ASD) being an important research topic. Several research groups have shown that 12.8-29 % of NF1 children score in the severe/clinical range on the Social Responsiveness Scale (SRS), an internationally accepted screening questionnaire for ASD (Adviento et al., 2014; Garg et al., 2013a; Plasschaert et al., 2014; Walsh et al., 2013). When focusing on systematic and multidisciplinary clinical ASD assessment using gold standard instruments, Garg and colleagues (2013b) and Plasschaert and colleagues (2014) reported a 25-26% prevalence estimate of ASD in the NF1 population.

Cognitive impairments are observed in up to 80 % of NF1 children. Many studies report an average left shift in IQ (+/- 10 IQ points lower), with specific problems in visual-perceptual abilities as a hallmark in NF1 (Hyman et al., 2005). In addition, deficits in other neuropsychological domains, such as attention, memory, Executive Functioning (EF), language and motor skills, are observed (Hyman et al., 2005; Levine et al., 2006). It is assumed that these behavioral and cognitive problems contribute to poor quality of life for people with NF1 and are a major concern for parents and teachers (Graf et al., 2006).

Our study focuses on *EF* in NF1 children. In general, EF is described as an umbrella term covering several interrelated but distinct higher-order cognitive functions, serving goal-oriented regulation of thoughts and actions (Denckla, 1996; Miyake & Friedman, 2012). However, many different definitions co-exist and there is no consensus on the constituting factors. Different factor-analytic studies have yielded different results, depending on the measures included in the analyses (Jurado & Rosselli, 2007). The three most commonly dissociated factors are inhibition (the ability to suppress a certain behavior or to ignore distracting information), working memory (the ability to hold certain information active while performing a task) and cognitive flexibility (or set-shifting:

the ability to shift between different thoughts or actions) (Diamond, 2013; Miyake & Friedman, 2012; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Additional often studied EFs are generativity (or fluency: the ability to generate novel ideas) and planning (the ability to look ahead before starting to perform a task) (e.g. Hill, 2004; Jurado & Rosselli, 2007; Pennington & Ozonoff, 1996; White, 2013). Here, we focus on these five EF domains.

Several research groups have demonstrated that children with NF1 have difficulties in multiple EF domains, with daily life EF as well as laboratory test performance being impaired. When measuring EF abilities in *daily life*, by using the Behavior Rating Inventory of Executive Function (BRIEF), problems in EF were observed for all relevant subscales by Payne et al. (2011). However, other authors only observed problems with cognitive flexibility (Pride et al., 2010), planning/organization (Gilboa et al., 2014) and working memory (Gilboa et al., 2014; Sangster et al., 2011; Ullrich et al., 2010). When reviewing research using *more structured, laboratory tasks*, a wide range of executive dysfunctions has been reported. Deficits in *inhibition* have most frequently been observed using several continuous performance tasks, which also require sustained attention and attentional shifting (Ferner et al., 1996, Gilboa et al., 2011; Huijbregts et al., 2010; Isenberg et al., 2013; Mautner et al., 2002; Rowbotham et al., 2009). In addition, problems with *cognitive flexibility* (Descheemaeker et al., 2005; Hofman et al. 1994; Rowbotham et al., 2009; Roy et al., 2014), verbal or spatial *working memory* (Champion et al., 2014; Ferner et al., 1996; Huijbregts et al., 2010; Payne et al., 2012; Rowbotham et al., 2009; Ullrich et al., 2010) as well as *planning* abilities (Galasso et al., 2014; Hofman et al., 1994; Hyman et al., 2005; Levine et al., 2006; Payne et al., 2011; Pride et al., 2010; Roy et al., 2010) have been demonstrated. However, no difficulties in *fluency* were previously reported in the NF1 literature, based mainly on verbal fluency tasks (Hofman et al., 1994; Hyman et al., 2005; Payne et al., 2011; Roy et al., 2014) with one study also demonstrating intact design fluency (Roy et al., 2014).

Although several studies have shown EF impairments in children with NF1, the findings remain inconclusive. This is largely due to (at least) one of the following study limitations. Firstly, since EF tasks always require a combination of EF and non-EF processes, this often precludes an unequivocal interpretation of research findings. This is also referred to as the task impurity problem (Jurado & Rosselli, 2007; Miyake & Friedman, 2012). Secondly, most studies included a rather small NF1 (and typically developing (TD)) group. Therefore, group differences may have been missed due to a lack of statistical power. Thirdly, most studies only investigated a subset of the five above-mentioned EF domains. However, since different samples are included in different studies and differences in sample characteristics (e.g. age and IQ) might influence research findings, a broader picture of the EF profile of individuals with NF1 is preferably obtained within the same sample. Finally, although some studies consider the level of intellectual functioning of participants in their analyses, none of the above-mentioned studies accounted for the higher prevalence of ASD or ASD symptoms in NF1. Since individuals with ASD also show EF impairments (for reviews see Brunsdon & Happé, 2014; Geurts, et al., 2014; Hill, 2004) and increased ASD symptoms are related with reduced EF performance (Brunsdon & Happé, 2014; Van Eylen et al.,

2015), it remains unclear which EF impairments of individuals with NF1 are specific to this disorder compared to ASD and whether EF impairments in NF1 compared to TD individuals remain after controlling for group differences in ASD symptoms.

The goal of this study was to overcome the above-mentioned shortcomings of previous studies. More specifically, we aimed to reduce task impurity and to systematically investigate five EF domains (inhibition, cognitive flexibility, working memory, generativity and planning) in a large sample of NF1 children and adolescents, while controlling for IQ and ASD symptoms.

To reduce task impurity we administered an extended test battery specifically designed for this aim (Van Eylen et al., 2015). This battery allows to control for the contribution of possible confounding EF and non-EF variables in various ways. Firstly, we selected tasks with a within-subject design where we compared performance on two task conditions that share the non-EF requirements, but differ in the particular EF process. Calculating the difference score between both conditions then yields a more valid measure of that particular EF ability. Secondly, we looked for converging evidence. Convergence is obtained when different instruments assessing the same EF yield the same findings. Selecting highly differing instruments that claim to assess the same underlying EF ability increases the probability that convergent deficits are due to an actual EF impairment and not merely to a deficiency in any of the additional non-EF processes. We therefore measured each EF domain with several instruments tapping into different additional processes. Thirdly, when a particular EF deficit is found, we sought to dissociate it from any confounding variables. If no group differences are found on any of the possibly confounding variables, this provides further evidence that the group difference on the EF task is genuinely due to differences in a specific EF. Confounding variables comprise various non-EF and EF abilities. For example, Miyake and Friedman (2012) suggested that inhibition is a common component in all EF tasks. In a previous study we determined the *potential EF confounds* for all main laboratory EF measures, by calculating the correlations between them (Van Eylen et al., 2015). We also included several *control measures of non-EF abilities*[1] that are involved in the EF tasks (like motor or processing speed). Finally, if group differences were also found on possible confounding (EF and/or non-EF) variables, we investigated whether EF impairments remained while statistically controlling for these confounds (by including them as a covariate in the analyses).

The performance of individuals with NF1 was compared with age- and gender-matched TD children. However, in line with previous studies (see above), our NF1 sample showed a significantly lower average IQ and increased ASD symptoms, compared to the TD group (see Table I). Since these factors may influence their EF abilities, we explored whether group differences remained after controlling for these potentially confounding variables. Concerning IQ, a lower score has been associated with reduced performance on EF tasks (Arffa, 2007; Friedman et al., 2006). However, not all EF domains have been found to correlate with IQ and the strength of the correlation appears to be task dependent (Friedman et al., 2006; Van Eylen et al., 2015). Furthermore, although

[1] Whether or not these control measures require non-EF and/or other EF abilities may be debatable and depends on the applied definition and conceptualization of EF.

Levine et al. (2006) strongly recommend to control for IQ, this has been debated (Dennis et al., 2009). We therefore also reported the results without correction for IQ. Moreover, given the high co-occurrence of NF1 and ASD and knowing that both disorders are associated with EF impairments, we wanted to investigate which EF impairments are specific to individuals with NF1 compared with an age- and gender-matched ASD group. A comprehensive understanding of EF deficits in individuals with NF1 is essential to develop successful and specific interventions.

MATERIALS AND METHODS

Participants

All participants were between 8 and 18 years old, had a full scale IQ (FSIQ) above 70, and were Dutch-speaking. They all belonged to one of the three following groups: NF1, TD or ASD .

The *NF1 group* comprised 42 children that were recruited from our monthly outpatient Neurofibromatosis Clinic at the Department of Clinical Genetics, University Hospital Leuven. They all fulfilled the diagnostic criteria for NF1 specified by the NIH (1988). Sixteen NF1 children had a co-occurring ASD diagnosis. The *TD group* consisted of 52 children, who were recruited through schools, personal contacts and advertisements. According to parental reports, none of the TD children or any of their first-degree relatives presented with a neurological or psychiatric disorder. Furthermore, the absence of moderate or severe ASD characteristics was reflected by a T-score on the SRS (Dutch version, Roeyers et al., 2011) below 70 for all TD children. In the 52 children of the ASD group, the diagnosis of ASD was made by a multidisciplinary team according to DSM-IV-TR criteria (American Psychiatric Association, 2000) and confirmed by the Developmental, Dimensional and Diagnostic Interview (3di; Skuse et al., 2004). These children were recruited from the database of the Autism Expertise Centre at the University Hospital Leuven.

The groups were group-wise matched for age ($p = .69$) and for gender ratio ($p = .98$), but differed significantly for FSIQ ($p < .001$), verbal IQ (VIQ; $p < .001$), performance IQ (PIQ; $p < .001$), and ASD symptomatology as measured by the SRS total raw score ($p < .001$). Descriptive statistics for the demographic variables of the groups are displayed in Table I.

Informed consent was obtained from the participants' parents and the study was approved by the Medical Ethical Committee of the University Hospital Leuven (S54630 - ML8783) and the Ethical Committee of the Faculty of Psychology and Educational Sciences of the KU Leuven.

(Insert Table I)

Measures

Intellectual functioning. Intellectual functioning was estimated with an abbreviated version of the Dutch Wechsler Intelligence Scale for Children (WISC-III-NL; Kort et al., 2005) or Wechsler Adult Intelligence Scale (WAIS-III-NL; Wechsler, 2005), containing four subtests: Vocabulary, Similarities, Picture Completion and Block Design (Sattler & Saklofske, 2001). The first two subtests provided an estimate of VIQ, while the other subtests provided an estimated PIQ. Averaging VIQ and PIQ resulted in an estimate of FSIQ.

ASD symptomatology. The *Social Responsiveness Scale* (SRS) for children and adolescents is a normed questionnaire developed to assess a wide range of characteristics of ASD (Dutch version, Roeyers et al., 2011). It consists of five so-called treatment scales: social awareness, social cognition, social communication, social motivation and autistic mannerisms. By applying factor-analysis, Frazier et al. (2014) demonstrated that a 2-factor model, dividing SRS social and autistic mannerisms scales consistent with DSM-5 'Social Communication/Interaction' and 'Restricted and Repetitive Behaviors and Interests (RRBIs)' domains, best explains the variance in SRS scores. Accordingly, we summed the raw scores of the social treatment scales to obtain one index of social (communication and interaction) problems, while the raw score on the mannerisms scale was taken as an index of RRBIs. The total raw score was used as a covariate in our group analyses (see data analysis section).

EF and control measures. Five EF domains (inhibition, cognitive flexibility, generativity, spatial working memory and planning) and control measures were assessed with an extensive neurocognitive test battery developed by Van Eylen et al. (2015). In Table II, an overview of these instruments is presented together with their outcome measures. In what follows, each of these instruments is briefly described. First we present the laboratory tasks per EF domain, followed by a description of the questionnaire measuring EF in daily life and a control task. For more detailed information, see Van Eylen et al. (2015).

Inhibition was measured with a Go/No-Go task and a Flanker task. The computerized Go/No-Go task measures pre-potent response inhibition. On each trial, one of the following stimuli was presented: a triangle (20%), square (60%) or circle (20%). Participants had to press the response button as fast as possible (i.e. a Go-trial), except when a triangle was displayed (i.e. a No-Go-trial). The inhibition outcome variable is the percentage No-Go errors. The Flanker task measures resistance to distractor interference. A target stimulus (an arrow pointing left or right) was displayed and participants had to press the corresponding response button (left or right, respectively). On compatible trials the target was flanked by four arrows (two on each side) pointing in the same direction as the target (←←←←← or→→→→→). On incompatible (inhibitory) trials, the target was flanked by four arrows pointing in the opposite direction (→→←←← or ←←→←←). As outcome measure the inhibition cost was defined as the mean RT and error percentage on incompatible minus compatible trials. The mean RT on the compatible trials is considered a baseline control measure.

To measure *cognitive flexibility*, we administered the Wisconsin Card Sorting Task With Controlled Task Switching (WCST-WCTS) (Van Eylen et al., 2011) and an adapted version of the Switch task (Rubia et al., 2007).

In the WCST-WCTS, the influence of confounding variables is minimized, compared to the original WCST, by reducing social demands, working memory and generativity load, and by providing a within-subject calculation of the switch cost. On each trial, three cards were presented on a computer screen: one at the top and two at the bottom. Participants had to indicate which of the two cards at the bottom matched the card at the top, based on either color or shape. The correct sorting rule was not made explicit, but had to be derived based on feedback. The sorting rule changed without explicit warning after a variable number of consecutive correct trials. The main outcome measures are the mean number of perseverative errors and the switch cost RT (switch trial RT minus maintain trial RT). On the Switch task participants watched a grid divided into four squares with a double-headed arrow in the center pointing either horizontally or vertically. As soon as a red dot appeared in one of the four squares, participants had to press the button corresponding with the position of the dot, on a diamond-like four-button response box. After two to seven repeat trials a switch trial occurred with the direction of the arrow changing position. The main outcome measures are the switch cost RT and the switch cost error percentage (switch trial error percentage minus maintain trial error percentage). For both cognitive flexibility tasks, the RT on the maintain trial is considered a baseline control measure.

Generativity was assessed with the Uses of Objects task (Turner, 1999) and the Design Fluency test of the Delis-Kaplan Executive Functions System (D-KEFS, Delis et al., Dutch adaptation, Noens & van Berckelaer-Onnes, 2007a). The Uses of Objects task measures the ability to generate new ideas (ideational fluency). Participants were asked to generate as many useful uses as they could for six different objects. Scoring differentiated correct, incorrect (not useful, implausible or vague responses, or when merely a description of the object was provided), redundant and repetition (a literal repetition of a previous idea) responses. The number of correct responses is the main outcome measure, counted for all the items combined. Additionally, we calculated the total number of responses, and the percentage of incorrect, redundant and repetition responses. The first condition of the Design Fluency test provides a basic measure of design fluency. In this condition, rows of boxes were presented on a piece of paper, with each box containing the same array of black dots. The participant had to draw a different design in each box by connecting the dots using four straight lines and each line had to touch at least one other line at a dot. The reported outcome measure is the number of unique and correct designs.

Spatial working memory was measured with the Spatial Working Memory test of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cognition Cambridge, 1996) and the Spatial Span subtest of the Wechsler Non Verbal-NL (Wechsler & Naglieri, 2008). In the Spatial Working Memory test a number of boxes (4, 6 or 8) was presented on a touch screen and the participant had to find a ‘token’ in each of them by touching the correct box. Only one token was hidden at a time, and within the same trial it was never hidden in the same box again. A trial terminated when the token was found in each of the boxes. An error was defined as the selection of a box which did certainly not contain a token, either because the participant revisited a box in which a token was previously found or because the participant revisited a box that was already found to be empty during the same search. The main outcome measure is the total number of errors. Since an organized search strategy can minimize working memory load, a summary index of the applied strategy (i.e. the number of search sequences starting with a different box) was also registered as a control measure. On the Spatial Span test

a board containing 10 blocks in a specific configuration was placed in front of the participant. After the experimenter tapped a number of blocks, the participant had to touch the same blocks, either in the same order (forward condition) or in reversed order (backward condition). The number of correct trials was counted for both conditions combined.

Planning was assessed with the Tower test of the D-KEFS (Delis, et al., Dutch adaptation, Noens & van Berckelaer-Onnes, 2007b). Participants had to build a designated tower in as few moves as possible by moving five disks varying in size across three pegs, while moving only one disk at a time and never placing a larger disk on a smaller one. At the beginning of each trial, the experimenter placed a number of disks on the pegs in a predetermined starting position and displayed a picture showing the ending position of the disks. The move accuracy ratio (the actual number of moves divided by the number of minimally required moves) reflects the effectiveness of the employed strategy. Additionally, we assessed the time needed to make the first step (first step latency) and the mean time per step.

The Behavior Rating Inventory of Executive Function (BRIEF, Dutch version, Smidts & Huizinga, 2009) is a parent-report questionnaire assessing impairments in EF in daily life. We report the raw scores on the four subscales that match with the delineated EF domains: Inhibition, Shifting (flexibility), Working Memory and Planning.

The Motor Screening test is part of the CANTAB (Cognition Cambridge, 1996) and screens for basic visual, motor and task comprehension difficulties. Participants had to touch a cross, displayed at different locations on a touch screen, as fast as possible. Response latency of the correct trials was recorded. Processing speed was reflected by the RTs on the compatible trials of the Flanker task and on the maintain trials of the WCST-WCTS and Switch task.

(Insert Table II)

Procedure

Questionnaires were filled out by the parents (mother and/or father) of all participating children. All participants were individually tested for four hours (four 1-h sessions) in a quiet room, either at the University Hospital or at school. Computerized tasks were run on a Dell Latitude E6400 notebook. Stimuli of the Go/No-Go, Flanker and Switch tasks were presented on the notebook's screen. For the other computerized tasks, a 17-inch Elo Entuitive touch screen was used. To avoid fatigue, enough breaks and variation in task format were provided. The order of sessions and the order of tasks within a session were counterbalanced. Participants received a small reward for their participation.

Data analysis

Data were analyzed with SPSS version 20 (SPSS Inc., Chicago IL, USA). Prior to analysis, appropriate transformations (square root or logarithm base 10) were applied if necessary to obtain normally distributed variables. In the tables, the values for the mean and standard deviations were calculated for the raw, non-transformed variables. For the RT data, only the correct trials were used and within-subject outliers (>2.5 *SD* of the participant's own mean) were excluded.

For all measures, the performance of the three groups was compared (NF1, TD and ASD) with an ANOVA test. To specifically investigate the differences between the NF1 vs. TD group and between the NF1 vs. ASD group, these contrasts were calculated and Tukey-Kramer corrections were used to correct for multiple comparisons. For all EF measures and control variables we additionally performed ANCOVA analyses. First, we introduced IQ as a covariate. Since most EF and non-EF measures are based on performance tasks, we used PIQ as a covariate. Only for the Uses of Objects task we corrected for VIQ instead, because this is a verbally mediated task. Secondly, only SRS total raw score was included as a covariate, to control for group differences in ASD symptoms. Thirdly, analyses were performed including both covariates, whenever a group difference was found after controlling for one of the covariates. Moreover, if group differences were found on a particular EF measure and on corresponding confounding variables[2], we investigated whether the group differences on the EF measure remained after controlling for these confounds (in line with Van Eylen et al., 2015).

For all EF and control measures, Cohen's *d* effect sizes were calculated by dividing the difference between the groups' means by the pooled standard deviation. These values were calculated on the variables used for the ANOVA (non-transformed or after square root or logarithm base 10 transformation). An effect size ranging from 0.2 to 0.3 is considered small, values around 0.5 are medium and values of 0.8 or above are considered large effects (Cohen, 1988). A significance level of $p < 0.05$ (two-sided) was adopted for all analyses.

RESULTS

Descriptive statistics and group comparisons for the main EF measures are displayed in Table III, and results for the additional EF and control measures are presented in Table IV. Table V shows results for the daily life EF measures. Corresponding effect sizes are displayed in Figure 1 and Table IV. Significant differences of ANCOVA analyses, controlling for IQ and/or SRS total score, are also shown in Tables III, IV and V. Below, the results for the NF1 versus TD and for the NF1 versus ASD comparisons are described respectively.

(Insert Table III, IV and V and Figure 1 about here)

NF1 children compared to age- and gender-matched TD children

[2] The EF confounds were determined in a previous study by Van Eylen and colleagues (2015), based on the correlations between the laboratory EF measures.

Inhibition. On the *Go/No-Go task*, NF1 children had a higher percentage of No-Go errors compared to TD children, with a medium effect size. After controlling for *PIQ*, this group difference became marginally significant (p = .072) and it disappeared after controlling for *SRS total score*. On the *Flanker task*, the inhibition cost RT was higher in individuals with NF1 compared to TD individuals, with a medium effect size. After controlling for *PIQ*, this group difference remained significant, but not when controlling for *SRS total score*. Furthermore, no significant difference was observed for inhibition cost percentage of errors.

Cognitive flexibility. On the *WCST-WCTS*, the switch cost RT was similar in NF1 children compared to TD children. However, the NF1 group made significantly more perseverative errors than the TD group with a large effect size. Since both groups also differed on the control measure of this task (i.e. RT on maintain trials), and on possible EF confounds (i.e. inhibition: percentage No-Go errors; working memory: Spatial Working Memory total error score) we examined whether the group difference in perseverative errors remained after including all these confounding variables as covariates. This was the case (p = .009). Moreover, the difference in perseverative errors remained significant after controlling for *PIQ*, but not when including *SRS total score* as a single covariate. On the *Switch task*, the switch cost RT and percentage of errors were similar in both groups.

Generativity. Children with NF1 generated fewer correct answers on the *Uses Of Objects task* compared to TD children (large effect size), due to a higher percentage of redundant and incorrect responses (large and medium effect size respectively). However, the total number of responses and the percentage of literal repetitions were equal in both groups. After controlling for *VIQ or SRS total score*, all these group differences remained significant, with the exception of the amount of correct responses for which only a marginally significant difference was observed when correcting for SRS total score (p = .082). When including *both VIQ and SRS total score* as a covariate, all differences previously found for the additional outcome measures remained significant. Regarding performance on the *Design Fluency task*, NF1 children presented with fewer correct responses compared to TD children, with a medium effect size. However, this difference disappeared after controlling for an EF confound (i.e. working memory: Spatial Span correct trials; p = .559) or *PIQ* and was only marginally significant after controlling for *SRS total score* (p = .071).

Spatial Working Memory. On the *Spatial Working Memory task*, individuals with NF1 made significantly more errors in total compared to TD children (medium effect size). More specifically, NF1 children made more errors on the condition where 6 (p = .013) or 8 (p = .010) boxes were presented. However, the search strategy also differed significantly between both groups, and the group differences became non-significant after including this control measure, as well as an EF confound (i.e. cognitive flexibility: WCST-WCTS perseverative errors) as covariates (p = .24). Moreover, the difference in total errors score disappeared after controlling for *PIQ* and was only marginally significant after controlling for *SRS total score* (p = .051). Nonetheless, with the Spatial Span task a significantly reduced *Spatial Span* was observed in NF1 compared to TD children (large effect size), even

after including an EF confound (i.e. inhibition: percentage of No-Go errors), *PIQ* and *SRS total score* as single covariates.

Planning. On the *Tower task*, a significant group difference was observed for the move accuracy ratio when NF1 individuals were compared to TD children (medium effect size). This difference remained significant after controlling for an EF confound (i.e. cognitive flexibility: WCST-WCTS perseverative errors), and after accounting for *PIQ*, *SRS total score* and *both*. No group differences were observed on the additional measures of this task, namely the time to take the first step and the mean time per step.

EF in daily life: BRIEF. NF1 children had significantly higher scores,reflecting more EF problems, compared to TD children on the *BRIEF total raw score*, and the four reported subscales: *inhibition, flexibility, working memory* and *planning* (all with a large effect size). These significant differences remained after controlling for *PIQ*, but not when the difference in *SRS total score* was taken into account.

Non-EF control measures: Motor Screening and Processing Speed. No group differences were found on the *Motor Screening task* or on *Processing Speed* as measured with the switch task. However, processing speed as measured with the Flanker task (RT on compatible trials) and WCST-WCTS (RT maintain trials) yielded slower performance of NF1 compared to TD children (both with a medium effect size). After controlling for *PIQ*, only a marginally significant group difference in RT was found on the compatible trials of the Flanker task (p = .076), with no group differences remaining after controlling for *SRS total score*.

NF1 children compared to age- and gender-matched ASD children

Inhibition. On the *Go/No-Go*, no significant differences were found when NF1 children were compared to ASD children. Also on the *Flanker task*, NF1 children had a comparable inhibition cost percentage of errors. Nevertheless, there was a trend for a higher inhibition cost RT (p = .059; with a medium effect size). This trend became significant after controlling for *SRS total score* and also when additionally including *PIQ* as a covariate.

Cognitive flexibility. On the *WCST-WCTS* and the *Switch task*, no significant group difference was observed when NF1 children were compared to the ASD children. However, after including *PIQ* as a covariate, NF1 children showed a trend towards a lower switch cost RT on the WCST-WCTS compared to the ASD group. When controlling for *SRS total score*, this difference became significant and NF1 children also displayed more perseverative errors on the *WCST-WCTS* and on the *Switch task* we found a trend towards a lower switch cost percentage of errors (p = .059). After controlling for *both IQ and SRS total score*, the lower switch cost RT on the WCST-WCTS remained significant and we still found a trend towards a lower percentage of switch cost errors on the *Switch task* (p = .080).

Generativity. No significant differences were observed when NF1 children were compared to the ASD children on the *Uses Of Objects task* and the *Design Fluency task*. The same results were found after including *VIQ* (Uses Of Objects) or *PIQ* (Design Fluency) as a covariate. However, after controlling for *SRS total score*, a trend was found for less correct responses in the Uses Of Objects task for NF1 children ($p = .060$), combined with a lower number of responses compared to children with ASD.

Spatial Working Memory. On the *Spatial Working Memory task*, no significant group differences were observed, when NF1 children were compared to individuals with ASD. However, on the Spatial Span task NF1 children showed a reduced spatial span. This group difference disappeared after including *PIQ* as a covariate, but remained when controlling for *SRS total score*.

Planning. On the *Tower task*, no significant group differences were observed when NF1 individuals were compared to ASD children.

EF in daily life: BRIEF. Compared to ASD participants, NF1 children had significantly lower scores (suggesting less EF problems) on the *BRIEF total* and the *inhibition, flexibility* and *planning* subscales, with and without controlling for PIQ. After controlling for *SRS total score*, no group differences were found.

Non-EF control measures: Motor Screening and Processing Speed. NF1 and ASD children performed comparably on the *Motor Screening task* and all of the *Processing Speed* measures, with and without including *PIQ* as a covariate. However, after controlling for *SRS total score*, NF1 children performed significantly slower on compatible trials of the Flanker task.

DISCUSSION

In this study, we investigated EF abilities in a large sample of NF1 children by studying five EF domains (inhibition, cognitive flexibility, generativity, working memory and planning) with an extended battery of tests, designed to reduce task impurity. In the first part of this discussion, we will address EF deficits of NF1 children compared to TD children, and whether the group differences remain after accounting for the lower IQ of the NF1 children. In the second part, we will discuss the link between EF deficits in children with NF1 and their increased ASD symptoms. More specifically, we will address whether EF deficits of the NF1 children compared to the TD sample remain after controlling for ASD symptoms (as measured with the SRS) and which EF impairments are specific to the NF1 children compared to children with ASD.

EF in NF1 children vs. TD children and the influence of their lower IQ

Children with NF1 demonstrated significant EF impairments on all five EF domains, compared with TD peers. Most of these deficits remained significant or became marginally significant after including IQ as a covariate, suggesting that EF problems in NF1 children are not merely due to their lower level of intellectual functioning. Below we will first elaborate on the EF differences found on the laboratory tasks and afterwards discuss EF impairments on a questionnaire addressing daily life situations.

On the laboratory measures, problems in *cognitive flexibility* were observed in NF1 children, but only in a more unstructured, open-ended task where rule shifting is self-directed or internally controlled (WCST-WCTS), and not in a highly structured task assessing externally controlled rule shifting (Switch task). On the WCST-WCTS, NF1 children made more perseverative errors while no significant problem in switch cost reaction time was observed. This indicates that they made more errors while switching and that correctly switched trials are performed equally fast. Importantly, this difference in perseverative errors remained significant after controlling for several confounding variables (namely, their lower processing speed on this task (RT on maintain trials) and several EF confounds: reduced inhibition (percentage of No-Go errors) and spatial working memory (Spatial Working Memory total error score)), suggesting that it truly reflects a deficit in cognitive flexibility. Previous studies also showed deficits on several flexibility tests (Descheemaeker et al., 2005, Hofman et al., 1994; Rowbotham et al., 2009), but recently, Roy et al. (2014) criticized these findings for not being controlled for the lower intellectual functioning of NF1 children. In the latter study, deficits remained after controlling for IQ. Our study confirms these results, since NF1 children still made more perseverative errors, after inserting IQ as a covariate.

For *inhibition*, *generativity* and *working memory*, convergent evidence was found for an EF deficit, since two tasks per domain were included and NF1 children showed deficits on both tasks measuring the same domain. Concerning *inhibition*, deficits were found for both prepotent response inhibition (a higher percentage of No-Go errors on the Go/No-Go task), and resistance to distractor interference (a higher inhibition cost RT on the Flanker task). These findings are consistent with some studies showing more commission errors when the first type of inhibition was measured (Ferner et al., 1996; Gilboa et al., 2011; Isenberg et al., 2013; Mautner et al., 2002), while other studies indicated a higher error rate when the second type of inhibition was assessed (Huijbregts et al., 2010; Rowbotham et al., 2009). We also observed group differences in processing speed on one of the inhibition tasks (Flanker task). However, by calculating the inhibition cost on this task, we controlled for this potential confound and therefore showed that inhibition difficulties emerged on top of a slower general processing speed. Moreover, even after including IQ as a covariate, group differences for both types of inhibition were found (although the group difference in response inhibition (i.e. percentage of No-Go errors) was only marginally significant). Regarding *generativity or fluency*, NF1 children showed impairments on both a verbal (Uses of Objects) as well as a non-verbal (Design Fluency) fluency task. These results are in contrast with those of previous studies, reporting intact verbal and design fluency (Hofman et al., 1994; Hyman et al., 2005; Payne et al., 2011;

Roy et al., 2014). However, our verbal fluency task is less structured compared to the tasks used in previous studies and assesses more complex, ideational fluency instead of phonological and categorical fluency (Turner, 1999). Even after accounting for their lower VIQ, NF1 children performed weaker on this type of verbal fluency. Nonetheless, deficits in non-verbal design fluency disappeared after controlling for an EF confound (namely reduced working memory as reflected by less correct trials on the Spatial Span task) and when controlling for PIQ, indicating that reduced performance on this task was probably not due to impaired design fluency in children with NF1. Pertaining to *spatial working memory*, NF1 children performed less well than TD controls on the Spatial Working Memory task and on the Spatial Span test. On the Spatial Working Memory task group differences only emerged on the more difficult conditions (6 and 8 boxes). This finding is more or less consistent with a previous study using the same spatial working memory task (Payne et al., 2012), in which NF1 children only had problems when 8 boxes were present. Interestingly, we found that the group differences disappeared after controlling for additional impairments in search strategy and cognitive flexibility (WCST-WCTS perseverative errors), suggesting that reduced task performance of NF1 children might be due to a disorganized sequential search strategy and/or cognitive flexibility impairments rather than reduced working memory. Additionally, group differences disappeared after including PIQ as a covariate. Nonetheless, the group difference on the Spatial Span test remained after controlling for impaired response inhibition (percentage of No-Go errors) or PIQ. A possible explanation for the inconsistent findings for both tasks is that the latter task, although being more structured, requires more storage capacity combined with visuo-spatial-motor coordination, which seems to be a difficulty in NF1 children (Schrimsher et al., 2003). In contrast, the Spatial Working Memory task is assessed in a two-dimensional way on computer, which makes fewer visuo-spatial-motor demands.

Impairments in *planning* were also present, as individuals with NF1 had a higher move accuracy ratio on the Tower test. Since we found no group difference on additional measures, such as time per step and first step latency, impulsivity can be ruled out as a contributing factor. Furthermore, the group difference remained after controlling for possibly confounding impairments in cognitive flexibility or PIQ. These results confirm the findings of previous studies using the Tower as an assessment tool of planning abilities (Galasso et al., 2014; Hofman et al., 1994; Hyman et al., 2005; Levine et al., 2006; Payne et al., 2011; Pride et al., 2010) and are in line with a study of Roy et al. (2010), showing that differences still exist after controlling for lower intellectual functioning or basic skills.

A daily life EF measure showed that NF1 children have significantly higher scores compared to TD children on all relevant BRIEF scales, even after controlling for intellectual functioning. A functional questionnaire, such as the BRIEF, expands our knowledge on the cognitive profile of NF1 children by capturing difficulties in everyday naturalistic environments compared to a traditional neuropsychological test setting. Our findings are in line with the results found by Payne et al. (2011) and Roy et al. (2015), but contrast partially with studies in which no group differences were found on the inhibition and/or flexibility scale of the BRIEF (Gilboa et al., 2011; Pride et al., 2010).

Although some authors recommend to control for IQ (e.g. Levine et al., 2006), there is a debate on whether IQ should/could be included as a covariate or not. Dennis and colleagues (2009) argue that an IQ score postdates the condition and can therefore never be fully separated from the effects of the condition. As such, including IQ as a covariate provides too strict a control for the lower intellectual functioning of NF1 children and might therefore underestimate true EF impairments. However, we could argue that group differences that remain significant after controlling for IQ really show robust and genuine differences in EF. Furthermore, Dennis et al. (2009) demonstrated that in some cases controlling for IQ leads to counterintuitive findings about neurocognitive function (e.g. by enlarging group differences). As such, the results of analyses including IQ as a covariate should be interpreted with caution. Therefore, we also reported the results without controlling for IQ. Moreover, to further investigate whether EF impairments in NF1 children are not entirely attributable to their lower IQ, additional studies could include comparison groups matched for IQ (although Dennis et al., 2009, argue that matching for IQ has, at least partially, the same limitations as including IQ as a covariate).

Increased ASD symptoms in NF1 children and the link with EF deficits

In our NF1 sample increased ASD symptoms were observed compared to the TD group and 38 percent was formally diagnosed with ASD, matching the findings of previous studies (Garg et al., 2013a, 2013b; Plasschaert et al., 2014; Walsh et al., 2013). Since previous studies have shown that ASD symptoms are related to EF impairments (for reviews, see Brunsdon & Happé, 2014; Geurts et al., 2014; Hill, 2004), we investigated whether EF impairments in children with NF1 might be linked with their increased ASD symptoms. Concretely, we examined whether EF deficits of the NF1 children compared to the TD sample remained after controlling for ASD symptoms (as measured with the SRS) and whether some EF impairments are specific to NF1 children compared to children with ASD. Our results indicate that this is the case for some EF problems, suggesting that executive dysfunction is a core deficit in children with NF1 that is not solely attributable to their increased ASD symptoms.

Firstly, when we compared NF1 and TD children and controlled for the differences in ASD symptoms, NF1 children still displayed deficits in spatial working memory and planning and a trend towards a generativity impairment was found. Although these group differences could be due to a lower IQ in the NF1 group, the planning deficits remained significant after additionally controlling for this covariate. Secondly, when comparing the NF1 group with an *age- and gender-matched ASD group*, NF1 children showed a reduced spatial span and a trend towards a reduced ability to resist distractor interference on the Flanker task (one type of inhibition). Since these EF deficits were found despite significantly less ASD symptoms in NF1 compared to ASD children, this provides strong evidence that ASD symptomatology is not the main basis of these executive dysfunctions in NF1 and suggests that these EF impairments are a central characteristic of the disorder. Given the significantly lower ASD symptoms in NF1 compared to ASD children, we additionally investigated which group differences emerged *after controlling for SRS total raw score.* Besides the reduced spatial span and resistance to distractor interference, alterations in cognitive flexibility (with increased perseverative errors, but a reduced switch cost on the WCST-WCTS) were observed. These cognitive flexibility findings (increased perseverative errors with a reduced switch

cost on the WCST-WCTS) probably reflect a speed-accuracy trade-off. Furthermore, after additionally controlling for IQ, we still found reduced resistance to distractor interference and altered cognitive flexibility in NF1. Concerning cognitive flexibility, only the reduced switch cost and not the increased perseverative errors on the WCST-WCST remained significant, combined with a trend towards a lower percentage of switch cost errors on the Switch task. These findings might suggest that NF1 children are somewhat better in cognitive flexibility compared to children with ASD.

Intriguingly, regarding EF in daily life we found that NF1 children had more EF problems than TD children and less than ASD children. This pattern of findings nicely mirrors the group differences in ASD symptomatology and the highly significant EF differences became non-significant after controlling for this factor (SRS score). However, the implications of these findings are less clear. On the one hand, they indicate that parent reports about EF in daily life are strongly associated with the level of ASD symptoms, with children having more ASD symptoms being perceived as having more EF difficulties. On the other hand, it could be that the EF impairments in NF1 children are perceived as less salient by their parents, because they occur alongside other more severe impairments compared to those of the ASD children.

This is the first study investigating the association of increased ASD symptoms in NF1 children with their EF impairments. Recently, several research groups observed difficulties in social functioning as a prominent feature of children with NF1 and a high co-occurrence with ASD (Adviento et al., 2014; Garg et al., 2013a, 2013b; Plasschaert et al., 2015; Walsh et al., 2013). Moreover, Huijbregts et al. (2011) showed important associations between measures of cognitive ability and social (dys)functioning. Nevertheless, some studies have already accounted for the co-occurrence of NF1 with ADHD (Lidzba et al., 2012; Payne et al., 2012; Roy et al., 2010, 2014; Rowbotham et al., 2009). For example Roy and colleagues (2010, 2014), demonstrated that the impact of ADHD symptomatology on EF in NF1 is limited. Here, we provided further insights into the EF abilities of NF1 children, by demonstrating that their EF impairments are also not solely attributable to their increased ASD symptoms. These findings further strengthen the idea that executive dysfunction is a core deficit in NF1 children.

However, the results of the analyses controlling for ASD scores should be interpreted with caution. If NF1 is causally related to increased ASD symptoms (as earlier studies seem to suggest), then controlling for ASD symptoms artificially reduces impairments intrinsically related to NF1, when comparing NF1 and TD children. On the contrary, since NF1 children displayed fewer ASD symptoms compared to children with ASD, controlling for these differences might overestimate EF impairments in the NF1 group compared to the ASD group. Furthermore, although it is clear that EF and ASD symptomatology are highly associated, the direction of the supposed causal relationship is less straightforward. It could be that a mutation in the NF1 gene causes EF impairments as well as ASD symptoms, inducing a spurious correlation between EF and ASD characteristics. Another possibility is that an NF1 mutation causes EF impairments and that these deficits cause or at least contribute to ASD symptomatology. This last reasoning is in line with the EF theory of ASD, which proposes that EF dysfunction underlies at least some symptoms of ASD (Brunsdon & Happé, 2014; Hill, 2004). If this is the

case, statistically controlling for ASD symptoms masks EF impairments that are in fact a central characteristic of NF1. We therefore argue that additional (e.g. longitudinal) research is needed to investigate the influence of increased ASD symptoms on the EF profile of NF1 individuals. It would also be interesting to compare an NF1 sample without co-occurring ASD with an IQ-, age- and gender-matched NF1 sample with co-occurring ASD and with a TD group. This requires extensive clinical assessment of all participants for ASD symptoms. In this study, some children in the NF1 group had already received an ASD diagnosis, but not all of them were extensively assessed, making it uncertain whether the other NF1 individuals also have ASD or not. Also note that an NF1 sample without co-occurring ASD is not representative for the entire NF1 population. A study by Plasschaert et al. (2015) demonstrated that 63% of the NF1 sample showed increased ASD symptoms, as measured with the SRS (in line with Garg et al., 2013a, 2013b; Walsh et al., 2013). This indicates that NF individuals without increased ASD symptoms are a minority, making it very difficult to recruit sufficiently large samples.

Study limitations and further directions

This study offered a more advanced insight into the EF impairments of NF1 children. However, several limitations should be addressed and several issues are still awaiting further exploration. Here, we list a few prominent ones. First, the NF1 children with co-occurring ASD were originally recruited for another study. We then additionally tried to recruit individuals without co-occurring ASD to obtain a representative NF1 sample, which may have induced a selection bias and overrepresentation of ASD. Nonetheless, the distribution of ASD symptoms in this NF1 study group was comparable with the distribution measured in a generally screened NF1 clinical population (Plasschaert et al., 2015). Secondly, 8-to-18 year old children and adolescents with an IQ above 70 participated in this study; it therefore remains to be shown whether our findings can be generalized to individuals outside this age and IQ range and whether the EF profile is the same for children compared to adolescents. Thirdly, our comparison groups differed from the NF1 group in terms of IQ and ASD symptoms. To investigate the influence of these factors on the EF profile of NF1 individuals, both variables were included as a covariate. However, as mentioned previously, these findings should be treated with caution. We therefore encourage additional studies to circumvent this problem. However, this is not easy given that a lower IQ and increased ASD symptoms could be inherently related to NF1 (Garg et al., 2013a, 2013b; Hyman et al., 2005; Plasschaert et al., 2015; Walsh et al., 2013). It would be interesting to see how our results compare with those of studies including samples matched for IQ. Moreover, comparing thoroughly assessed NF1 groups with and without co-occurring ASD would also provide more insight into the effect of additional ASD symptoms on EF in NF1 individuals. Fourthly, although a great contribution of this study is that it investigates the influence of IQ and ASD symptomatology on EF in NF1, there are other factors known to influence EF that were not taken into account, for example, socioeconomic status (SES; for a review see Hackman & Farah, 2009) and ADHD symptomatology (Willcutt et al., 2008). Concerning SES, the cause of the association with EF is not clear (Hackman et al., 2010, 2015). For example, a higher SES is also associated with a higher IQ (Hackman et al., 2010), which in turn has been associated with better EF (or at least some aspects of it, Arffa, 2007; Friedman et

al., 2006). In this study we decided to only control for IQ and not additionally accounted for SES. Concerning ADHD symptomatology, some studies have already accounted for the co-occurrence of NF1 with ADHD when studying EF (Lidzba et al., 2012; Payne et al., 2012; Roy et al., 2010, 2014; Rowbotham et al., 2009). However, it would be interesting to take into account both ASD and ADHD features. Unfortunately, systematically collected ADHD measurements were absent in our total group of NF1 children. Finally, NF1 children are known to have a very heterogeneous cognitive profile. Investigation of individual EF profiles and delineation of subgroups (e.g. linked with distinct types of NF1 mutations, age, co-occurrence of ADHD/ASD, etc.) may be an interesting future approach.

General conclusions

This study strengthens the idea that executive dysfunction is a core deficit in NF1 children and makes a significant contribution to the existing literature on EF in NF1 in several ways. First, since we controlled for possible confounding (EF and non-EF) variables, we reduced EF task impurity and provided strong evidence that reduced task performance in children with NF1 reflects EF dysfunction. Overall, when comparing the performance of NF1 and TD children, we found impairments in all EF domains. More specifically, children with NF1 showed deficits in inhibition (both response inhibition and distractor interference) and planning, whereas EF impairments in the other domains seem to depend on specific task characteristics or are restricted to a certain EF subtype. Group differences in cognitive flexibility were only found on an open-ended task, generativity deficits seem to be restricted to verbal ideational fluency (with probably intact non-verbal design fluency) and spatial working memory impairments only survived statistical control for confounding variables on a task placing high visuo-spatial-motor coordination demands. Furthermore, the NF1 children displayed profound EF impairments in daily life. All these group differences remained significant after accounting for the lower intellectual functioning of the NF1 children (with the exception of response inhibition for which only an insignificant trend was observed). Second, this is the first study investigating whether EF deficits in children with NF1 might be due to their increased ASD symptoms. Our results indicate that although EF is highly associated with ASD symptomatology, this is not the main basis of all executive dysfunctions in NF1, suggesting that at least some EF impairments are a central characteristic of the disorder. More specifically, we found reduced spatial span and planning in NF1 children compared to TD children, when controlling for ASD symptoms. Compared to children with ASD, children with NF1 showed reduced spatial span and we found indications for reduced distractor interference and altered (possibly better) cognitive flexibility.

Nevertheless, this study has its limitations and other studies are needed to replicate and extend our findings.

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All authors declare that there is no conflict of interest.

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Table I

Characteristics of all participating children group-wise matched for age and gender

Characteristics	NF1 (*n* = 42: 26 M, 16 F)	TD (*n* = 52: 32 M, 20 F)	ASD (*n* = 52: 32 M, 20 F)	ANOVA		Post-hoc Tukey-Kramer correction	
	Mean (*SD*)			*F*	*p*	NF1 vs. TD *p*	NF1 vs. ASD *p*
Age (years)	12.48 (3.08)	12.27 (2.65)	12.00 (2.42)	0.368	.69	-	-
FSIQ	89.73(12.16)	109.91 (10.86)	102.16 (12.44)	34.11	**< .001**	**< .001**	**< .001**
VIQ	91.93 (13.64)	114.12 (13.40)	101.81 (16.85)	26.59	**< .001**	**< .001**	**004**
PIQ	87.52 (13.87)	105.71 (14.41)	102.52 (14.36)	20.96	**< .001**	**< .001**	**< .001**
SRS total [a]	62.05 (29.48)	18.52 (13.37)	101.33 (23.94)	177.40	**< .001**	**< .001**	**< .001**
SRS soc. problems [a]	53.12 (24.21)	16.98 (11.87)	83.96 (20.23)	162.16	**< .001**	**<.001**	**<.001**
SRS mannerisms [a]	8.93 (6.60)	1.55 (1.95)	17.37 (5.45)	151.09	**< .001**	**<.001**	**<.001**

NF1: Neurofibromatosis Type 1; TD: Typically Developing; ASD: Autism Spectrum Disorder; M: Male; F: Female; FSIQ: Full-Scale IQ; VIQ: Verbal IQ; PIQ: Performance IQ; SRS: Social Responsiveness Scale / [a] Data are missing from 8 TD participants

Table II

Overview of all EF and control measures per instrument and cognitive domain

Task/questionnaire per COGNITIVE DOMAIN	Instrument	Main outcome measures	Additional EF or control measures
EF TASKS:			
INHIBITION	Go/No-Go task	% No-Go errors	-
	Flanker task	Inhibition cost RT [a] Inhibition cost error % [a]	RT compatible trials [e]
COGNITIVE FLEXIBILITY	WCST-WCTS	Switch cost RT [b] Perseverative errors	RT maintain trials [e]
	Switch task	Switch cost RT [b] Switch cost error % [b]	RT maintain trials [e]
GENERATIVITY	Uses Of Objects task	Number of correct responses	Total number of responses % incorrect responses % redundant responses % repetitions
	Design Fluency test (D-KEFS)	Correct responses condition 1	-
SPATIAL WORKING MEMORY	Spatial Working Memory test (CANTAB)	Total errors (Errors on 4, 6, or 8 box trials)	Strategy [c]
	Spatial Span test (WNV-NL)	Correct trials	-
PLANNING	Tower test (D-KEFS)	Move accuracy ratio [d]	Time per step First step latency
EF QUESTIONNAIRE:	BRIEF (questionnaire)	Total score + subscales: inhibition, shift, working memory and plan/organize	
ADDITIONAL CONTROL TASK:			
BASIC VISUAL/MOTOR SCREENING	Motor Screening test (CANTAB)	Response latency	-

EF: Executive Functioning; RT: reaction time; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task switching; D-KEFS: Delis–Kaplan Executive Function System; CANTAB: Cambridge Neuropsychological Test Automated Battery; WNV-NL: Wechsler Nonverbal Scale of Ability – Dutch version; BRIEF: Behavior Rating Inventory of Executive Function – Dutch version

[a] Incompatible RT or error % minus compatible RT or error %

[b] Switch trial RT or error % minus maintain trial RT or error %

[c] The number of search sequences starting with a different box: does not measure spatial working memory, but provides a control measure for search efficiency

[d] Actual number of moves divided by number of minimally required moves

[e] Baseline control measure reflecting processing speed

Table III

Group comparisons for NF1 versus TD and NF1 versus ASD on the main EF outcome measures for each task and significant differences after

Measures per task	NF1 (n = 42)	TD (n = 52)	ASD (n = 52)	ANOVA		Post-hoc Tukey-Kramer correction	
		Mean (*SD*)		*F*	*p*	NF1 vs. TD *p*	NF1 vs. ASD *p*
INHIBITION							
Go/No-Go							
% No-Go errors	25.99 (17.48)	17.23 (12.01)	24.44 (15.42)	3.70	**.027**	**.047**	.970
Flanker							
Inhibition cost RT (ms) [a]	81.91 (100.52)	44.97 (29.26)	52.11 (48.39)	4.26	**.016**°■■*	**.017**°	.059■■**
Inhibition cost % errors [b]	4.09 (4.47)	2.53 (3.42)	3.75 (4.99)	1.74	.179	.198	.925
FLEXIBILITY							
WCST-WCTS							
Switch cost RT (ms) [c]	357.88 (368.48)	446.32 (312.67)	503.23 (299.80)	2.31	.103■■**	.396	.085■■***
Perseverative errors	2.68 (3.41)	0.88 (1.46)	1.66 (2.18)	9.08	**<.001**°■■	**<.001**°	.216■■
Switch							
Switch cost RT (ms) [b]	359.01 (126.86)	324.03 (111.85)	344.96 (126.67)	0.99	.373	.351	.844
Switch cost % errors	2.08 (5.39)	1.20 (3.21)	3.80 (5.74)	3.77	**.025**°	.658	.212
GENERATIVITY							
Uses of Objects [d]							
Correct responses	11.73 (5.62)	17.82 (7.54)	12.96 (6.23)	11.10	**<.001**°°°■	**<.001**°°	.655
Design Fluency							
Correct responses Condition 1	6.86 (3.70)	8.85 (2.89)	7.73 (2.51)	5.12	**.007**	**.005**	.348
SPATIAL WORKING MEMORY							
Spatial Working Memory [c]							
Total errors	40.79 (18.34)	28.04 (18.99)	36.86 (19.69)	5.64	**.004**	**.004**	.586
Spatial Span							
Correct trials	12.91 (4.23)	16.73 (3.02)	15.04 (3.55)	13.22	**<.001**°■■■	**<.001**°°■■■	**.013**■
PLANNING							
Tower							
Move accuracy ratio	2.14 (0.99)	1.74 (0.41)	1.89 (0.48)	3.72	**.027**■*	**.020**°■■**	.378

including IQ and/or SRS total raw score as a covariate

NF1: Neurofibromatosis Type 1; TD: Typically Developing; ASD: Autism Spectrum Disorder; WCST-WCTS: Wisconsin Card Sorting Task – With Controlled Task Switching / [a] NF1 group: n = 41, TD group: n = 51, ASD group: n = 51; [b] ASD group: n = 51; [c] TD group: n = 51, ASD group: n = 51; [d] NF1 group: n = 40, TD group: n = 49, ASD group: n = 48

Significant group differences (ANOVA) are shown in **bold**.

°($p < .05$), °°($p < .01$) or °°°($p < .001$): significant differences after including IQ as a covariate

■($p < .05$), ■■($p < .01$) or ■■■ ($p < .001$): significant differences after including SRS total raw score as a covariate

*($p < .05$), **($p < .01$) or ***($p < .001$): significant differences after including IQ and SRS total raw score as covariates

Table IV

Group comparisons for NF1 versus TD and NF1 versus ASD children on additional EF and control measures and significant differences after

	NF1 (*n* = 42)	TD (*n* = 52)	ASD (*n* = 52)	ANOVA		Post-hoc Tukey-Kramer correction			
						NF1 vs. TD		NF1 vs. ASD	
	Mean (*SD*)			*F*	*p*	*p*	Cohen's *d*	*p*	Cohen's *d*
Uses of Objects [a]									
Number of responses	34.80 (16.21)	39.08 (19.52)	39.08 (18.41)	0.57	.566$^{■*}$	.572	.22	.674$^{■}$	.17
% incorrect responses	44.33 (15.73)	36.15 (17.70)	46.08 (13.52)	5.42	**.006**$^{ºº■■**}$	**.043**$^{º■■*}$	.49	.862	.12
% redundant responses	19.59 (9.59)	12.03 (7.97)	17.40 (9.90)	7.41	**.001**$^{ºº■*}$	**.001**$^{ºº■*}$	.75	.674	.18
% repetitions	6.46 (6.15)	5.83 (5.83)	7.33 (6.54)	1.14	.324	.634	.20	.870	.11
Spatial Working Memory [b]									
Strategy	35.86 (4.29)	33.29 (5.40)	34.80 (3.95)	3.71	**.027**	**.022**	.53	.518	.26
Tower									
Time per step (sec)	3.66 (4.21)	3.45 (1.94)	3.41 (1.27)	0.41	.668	.801	.10	.652	.16
First step latency (sec)	4.43 (4.20)	3.82 (1.91)	4.60 (1.95)	2.32	.102	.794	.14	.369	.24
Motor screening [b]									
Response latency (ms)	840.52 (189.41)	823.63 (224.46)	828.69 (236.58)	0.17	.842	.839	.10	.897	.10
Processing speed (ms)									
Flanker RT compatible trials	536.99 (126.30)	471.46 (62.21)	497.65 (88.17)	5.74	**.004**$^{■}$	**.003**	.65	.109$^{■}$	.36
RT maintain trials									
WCST-WCTS [c]	1037.99 (326.93)	879.63 (250.91)	935.28 (283.92)	3.53	**.032**	**.025**	.54	.208	.34
Switch	554.27 (123.91)	535.48 (99.28)	561.27 (102.71)	0.78	.460	.680	.17	.948	.06

including IQ and/or SRS total raw score as a covariate

NF1: Neurofibromatosis Type 1; TD: Typically Developing; ASD: Autism Spectrum Disorder; WCST-WCTS: Wisconsin Card Sorting Task – With Controlled Task Switching / [a] NF1 group: *n* = 40, TD group: *n* =49, ASD group: *n* = 48; [b] ASD group: *n* = 51; [c] ASD group: *n* = 51, TD group: *n* = 51

Significant group differences (ANOVA) are shown in **bold**.

^{º}($p < .05$), ^{ºº}($p < .01$) or ^{ººº}($p < .001$): significant differences after including IQ as a covariate

$^{■}$($p < .05$), $^{■■}$($p < .01$) or $^{■■■}$ ($p < .001$): significant differences after including SRS total raw score as a covariate

*($p < .05$), **($p < .01$) or ***($p < .001$): significant differences after including IQ and SRS total raw score as covariates

Table V:

Group comparisons for NF1 versus TD and NF1 versus ASD children on daily life EF measured with the BRIEF and significant differences after including IQ and/or SRS total raw score as a covariate

	NF1 (*n* = 42)	TD (*n* = 50)	ASD (*n* =50)	ANOVA		Post-hoc Tukey	
	Mean (*SD*)			*F*	*p*	NF1 vs. TD *p*	NF1 vs. ASD *p*
BRIEF							
Total	136.00 (23.64)	108.04 (20.75)	153.18 (24.59)	48.27	**< .001°°°**	**< .001°°°**	**.002°°°**
Inhibition	17.33 (4.46)	13.61 (3.15)	19.68 (5.41)	23.39	**< .001°°°**	**< .001°°**	**.034°**
Flexibility	14.31 (4.06)	10.55 (2.57)	17.86 (3.54)	56.77	**< .001°°°**	**< .001°°°**	**< .001°°°**
Working memory	19.48 (4.49)	14.71 (4.21)	20.96 (5.34)	23.38	**< .001°°°**	**< .001°°**	.390
Planning	22.05 (4.65)	18.14 (4.17)	23.92 (5.15)	19.53	**< .001°°°**	**< .001°°**	**.039°**

NF1: Neurofibromatosis Type 1; TD: Typically Developing; ASD: Autism Spectrum Disorder; BRIEF: Behavior Rating Inventory of Executive Function
Significant group differences (ANOVA) are shown in **bold**.
°($p < .05$), °°($p < .01$) or °°°($p < .001$): significant differences after including IQ as a covariate
After including SRS total raw score as a covariate and after including both covariates, no significant differences were found

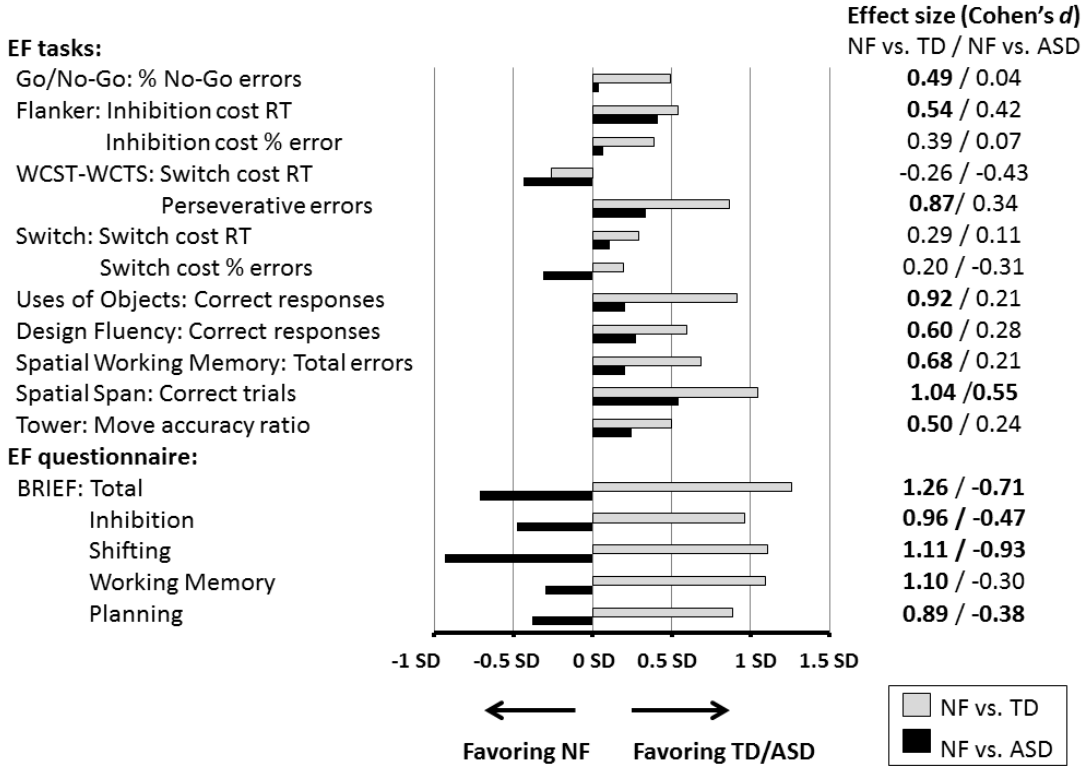

Figure 1. Cohen's *d* effect sizes for group differences in performance on the main EF measures. Bolded values indicate significant group differences. Positive scores indicate worse performance for NF1 children compared to TD or ASD children.